# OCCUPATIONAL METHAEMOGLOBINAEMIA

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Methaemoglobin is haemoglobin in which haem iron is oxidised to iron (III) and therefore cannot function as an effective oxygen transporting protein. Small amounts of methaemoglobin are produced continually, but the proportion of total haemoglobin that is present as methaemoglobin is maintained at around 1% by the action of an NADH dependent methaemoglobin reductase. A methaemoglobin concentration greater than 1% (methaemoglobinaemia) ensues if the rate of methaemoglobin formation exceeds its rate of reduction. Not only is methaemoglobin incapable of binding oxygen but, in addition, the oxidation of one or more of the haem iron atoms in the haem tetramer distorts the tetramer structure, so that the remaining non-oxidised haem subunits bind oxygen avidly but release it less efficiently, which shifts the oxygen dissociation curve to the left. Methaemoglobinaemia manifests therefore as tissue hypoxia.

## MECHANISMS OF METHAEMOGLOBIN FORMATION

The aetiology of methaemoglobinaemia may be congenital (for example, due to methaemoglobin reductase deficiency) or acquired (caused by exposure to oxidising chemicals or drugs). The mechanism of methaemoglobin formation has not been elucidated fully for all agents, but can be divided broadly into those that directly oxidise haemoglobin, those that indirectly oxidise haemoglobin, and those that require biochemical transformation to be capable of forming methaemoglobin.[1–3]

### Direct oxidation

Examples of compounds that are theoretically capable of oxidising haemoglobin directly include chlorates, hexavalent chromates, and copper (II) salts. Direct haemoglobin oxidation is dependent not only on the redox potential of the chemical agent relative to haemoglobin (agents with a higher redox potential than haemoglobin being capable of its oxidation), but also on the ability of the agent to penetrate red cells. Ferricyanide, for example, is capable of directly oxidising haemoglobin in vitro but cannot cause methaemoglobinaemia since it is unable to penetrate the erythrocyte membrane.[3] In addition, the redox potential of haemoglobin varies depending on its chemical conformation and on the prevailing physiological conditions. For example, the presence of co-factors such as 2,3-diphosphoglycerate and inositol hexaphosphate, increases the redox potential of haemoglobin. Moreover, direct haemoglobin oxidation reactions proceed much more readily in the absence of oxygen, a factor that explains in part why, under physiological (aerobic) conditions, methaemoglobinaemia is unusual following poisoning with hexavalent chromates[4] and usually only modest following poisoning with copper (II) salts.[5] The oxidation of haemoglobin by copper (II) is shown in fig 1. In this example the copper (I) produced can further react with oxygen to regenerate copper (II), so that under physiological conditions the redox reaction is prolonged.

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$$Cu^{2+} + HbFe^{2+} \longleftrightarrow Cu^{1+} + HbFe^{3+}$$

Figure 1   Direct haemoglobin oxidation by copper (II).

The predominant haematological effect in vivo in cases of severe poisoning with copper (II) salts (for example, copper sulfate),[5] hexavalent chromates,[6] and chlorates[7 8] is more typically intravascular haemolysis, sometimes with an intravascular coagulopathy, and these effects usually override those of methaemoglobin formation.

### Indirect oxidation

Indirect oxidation of haemoglobin involves a process of co-oxidation in which the methaemoglobin forming agent is co-oxidised with haem iron by haemoglobin bound oxygen ($HbO_2$). The reactive oxygen species, superoxide anion radical ($O_2^-$) and hydrogen peroxide

$$2HbFe^{2+}O_2 + 2NO_2^- \longrightarrow 2HbFe^{3+} + 2NO_3^- + O_2^{\cdot -} + e^- \qquad (1)$$

$$2NO_2^- + 2O_2^{\cdot -} + 6H^+ + 2e^- \longrightarrow 2NO + H_2O_2 + 2H_2O + O_2 \qquad (2)$$

$$2HbFe^{2+}O_2 + 2NO + e^- \longrightarrow 2HbFe^{3+} + 2NO_2^- + O_2^{\cdot -} \qquad (3)$$

$$H_2O_2 + 2NO_2^- \longrightarrow 2H^+ + 2NO_3^- + 2e^- \qquad (4)$$

The overall effect being:

$$4HbFe^{2+}O_2 + 4NO_2^- + 4H^+ \longrightarrow 4HbFe^{3+} + 4NO_3^- + 2H_2O + O_2 \qquad (5)$$

Figure 2   Indirect haemoglobin oxidation by nitrite.

($H_2O_2$), are produced when $HbO_2$ accepts electrons from ferrous haem and the methaemoglobin forming agent. Examples of compounds that oxidise haemoglobin indirectly are nitrites and phenylenediamines. The reactions involved are complex. They may result in the production of stoichiometric amounts of methaemoglobin (as occurs with nitrites), or may proceed in a cyclical fashion caused by regeneration of the methaemoglobin forming chemical (as occurs with phenylhydroxylamine).

Several mechanisms of indirect methaemoglobin formation by nitrite have been proposed.[2][3] All involve a lag phase followed by an autocatalytic or propagation phase which is dependent on production of the reactive oxygen species. One proposed reaction series[3] is summarised in fig 2. In this scheme superoxide anion radical reacts with nitrite to produce nitric oxide and hydrogen peroxide (line 2). Nitric oxide can then itself oxidise ferrous haem to produce methaemoglobin and superoxide anion radical (line 3). Though the nitrite and superoxide anion radical can then "feed back" into the reactions of lines 1 and 2, the formation of methaemoglobin by nitrite is a self limiting, stoichiometric process as represented in line 5. This is caused in part by the action of hydrogen peroxide as a nitrite scavenger (line 4).

Phenylhydroxylamine is a potent methaemoglobin forming compound. It enters an NADPH dependent redox cycle in which haemoglobin is oxidised and phenylhydroxylamine is reduced to nitrosobenzene (fig 3). As phenylhydroxylamine is regenerated in this cycle, a relatively small amount can produce a significant quantity of methaemoglobin before being lost to the cycle via a number of side reactions.

### Biochemical transformation

Many aromatic compounds, including the amino- and nitro-derivatives or benzene and related compounds, require biochemical transformation to become methaemoglobin forming agents. For example, aniline cannot oxidise haemoglobin directly, but is converted to phenylhydroxylamine by hepatic mixed function oxidase enzymes. Phenylhydroxylamine then enters the cycle of reactions outlined in fig 3. Nitrobenzene similarly requires metabolic transformation (via reduction to nitrosobenzene) in order to induce methaemoglobinaemia via the same cycle of reactions (fig 3).

Although a knowledge of the mechanisms of chemical induced methaemoglobin formation facilitates the prediction of chemicals likely to pose a risk of occupational methaemoglobinaemia, there remains considerable variation in methaemoglobin producing potential even between chemicals that appear to be closely related; this is explained in part by differences in metabolism. For example, p-dinitrobenzene is a more potent inducer of methaemoglobinaemia than is dinitrophenol since phenols are excreted more rapidly as glucuronides or sulfates via intrahepatic conjugation.[9] In addition, Cnubben et al showed that the pattern of substitution on a compound can influence its methaemoglobin forming potential by altering its
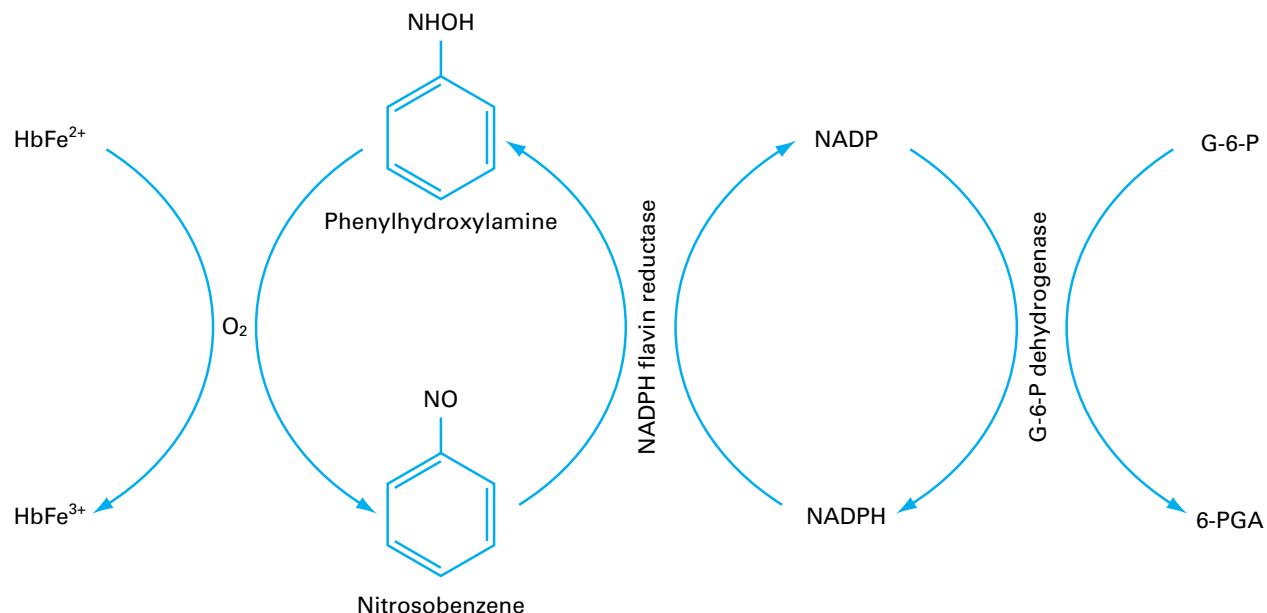


Figure 3   Cyclical methaemoglobin formation by phenylhydroxylamine.

vulnerability to alternative reaction pathways.[10] For example, increasing the number of fluorine substituents on fluorinated nitrobenzenes rendered the compound less susceptible to the nitro-reduction pathway that leads to methaemoglobin inducing metabolites and more susceptible to alternative reactions (with glutathione or other cellular nucleophiles) which do not produce methaemoglobin forming metabolites.

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**Box 1: Methaemoglobinaemia**

▶ Causes can be congenital or acquired from exposure to chemicals causing direct oxidation of haemoglobin, or indirect methaemoglobin formation
▶ Occupational cases are uncommon, but preventable
▶ Occupational cases have occurred in aniline dye and rubber manufacture, pharmaceutical, pesticide and electronics industry, transport and disposal of chemicals, and maintenance work
▶ A specific antidote (methylene blue) is available for severe cases, and prompt treatment will reduce morbidity and mortality
▶ Awareness of the condition and the importance of prevention and treatment will avoid cases being missed

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## Agents and industries

Most reported cases of occupational methaemoglobinaemia involve exposure to aromatic compounds, particularly amino- and nitro- substituted benzenes. Important qualities of these compounds are their high lipophilicity and volatility, which permit efficient dermal and inhalational absorption, the principal routes of occupational exposure. Moreover, these compounds can precipitate significant methaemoglobin formation from a relatively small amount of parent compound as described above. Inorganic and aliphatic compounds are implicated far less frequently.

In comparison to methaemoglobinaemia produced by accidental or intentional exposure to methaemoglobin forming drugs, methaemoglobinaemia resulting from accidental occupational exposure to chemicals is rare and not usually severe (methaemoglobinaemia < 20%). The few occupational cases that have been documented have occurred in aniline dye production,[11–13] in pharmaceutical,[14] pesticide[15] or rubber manufacture,[16] in the electronics industry,[17] during transportation or waste disposal of methaemoglobin forming agents[18] or in maintenance work.[19] Two case series reporting a total of 512 cases were published separately in 1964 and 1986.[11 13] Since 1987 there have been only 22 cases (10 reports) published.[14 16 18–25] This may be a result of improved provisions for health and safety at workplaces, or may reflect a reduction in the use of chemical agents known to cause methaemoglobinaemia.

## Clinical features

The clinical features observed at increasing methaemoglobin concentrations are summarised in box 2. It is important to remember that the "cyanosis" observed in mild methaemoglobinaemia is caused predominantly by the slate grey colour imparted by the methaemoglobin pigment rather than the presence of deoxygenated haemoglobin. A methaemoglobin concentration of 15% is equivalent to approximately 2 g/dl (assuming a total haemoglobin concentration of 13 g/dl), and this gives a degree of "cyanosis" equivalent to that seen in the presence of some 6 g/dl deoxygenated haemoglobin.

**613**

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**Box 2: Clinical features observed at increasing methaemoglobin concentrations**

| [Methaemoglobin] (%) | Features |
|---|---|
| 10–20 | Slate grey "cyanosis" |
| 20–40 | Headache, anxiety, dizziness, tachycardia |
| 40–60 | Lethargy, confusion, dyspnoea, respiratory depression |
| 60–80 | Arrhythmias, seizures, coma, death |

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Many of the chemicals that induce methaemoglobinaemia may also cause other physiological effects such that the clinical features observed may not be explained solely on the basis of methaemoglobin formation. Many nitrites (for example, sodium nitrite) are potent vasodilators causing headache, postural hypotension, and syncope in addition to methaemoglobinaemia. Oxidative denaturation of haemoglobin and oxidative damage to the red cell membrane may precipitate Heinz body haemolytic anaemia, a potentially life threatening complication of occupational poisoning with oxidising chemicals such as chlorates and aniline.

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**Box 3: Features of methaemoglobinaemia**

▶ A definite history of exposure to chemicals capable of inducing methaemoglobinaemia
▶ "Cyanosis" unresponsive to oxygen therapy
▶ Arterial blood samples showing normal partial pressures for oxygen and carbon dioxide
▶ High methaemoglobin concentration in arterial blood (key diagnostic feature)
▶ 15% methaemoglobin is approximately equivalent to 2 g/dl (1.2 mmol/l) methaemoglobin in a non-anaemic patient
▶ Metabolic acidosis may be present

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## Diagnosis and investigation of the cause

A definite history of exposure to an agent known to be capable of oxidising haemoglobin is usually present. An important clinical clue is that the patient appears cyanosed to an extent that is disproportionately greater than their degree, if any, of respiratory distress. Moreover, the cyanosis is unresponsive to oxygen therapy.

Pulse oximetry is unreliable in the presence of methaemoglobinaemia since oxygen saturation is determined by the ratio of light absorbance at two wavelengths (660 and 940 nm) and, unlike oxyhaemoglobin and deoxy-haemoglobin, methaemoglobin absorbs light almost equally at both wavelengths.[26]

Arterial blood drawn from a patient with significant methaemoglobinaemia appears chocolate brown and does not change colour on exposure to oxygen. Arterial blood gas analysis will show normal partial pressures of oxygen and carbon dioxide, even in the presence of high methaemoglobin concentrations, since these parameters reflect dissolved gas in the sample and are not affected by methaemoglobinaemia (the $P_{O_2}$ may even be increased if the patient is receiving supplemental oxygen). The blood gas analyser will display a falsely raised haemoglobin oxygen saturation that it calculates from the pH and $P_{CO_2}$, assuming normal haemoglobin is present. If there is significant tissue hypoxia, a metabolic acidosis may be present. An arterial
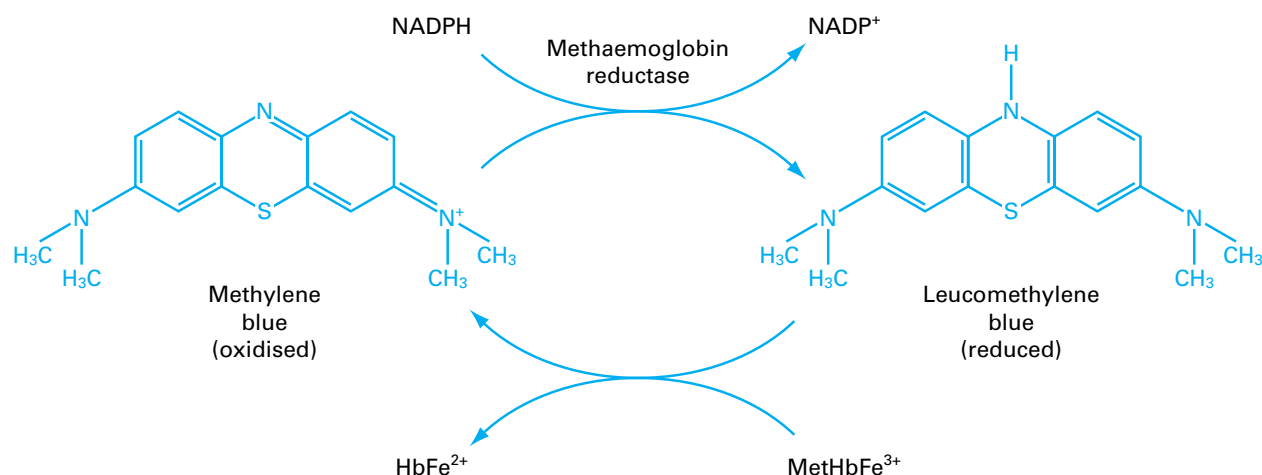
Figure 4   Mechanism of methaemoglobin reduction by methylene blue

methaemoglobin concentration will confirm the diagnosis and in practice it is not unusual for the diagnosis to be missed until this result is seen.

Every case of occupational methaemoglobinaemia should be investigated fully, since the factors leading to overexposure may potentially also affect other workers. The system of work should be reviewed, and improvements in the handling of chemicals considered.

## Management

The casualty should be removed from exposure, skin decontamination should be performed if appropriate, and supportive measures (including oxygen therapy if there is respiratory distress) should be instituted promptly.

### Methylene blue

Methylene blue acts as an electron donor in the non-enzymatic reduction of methaemoglobin (fig 4). An NADPH methaemoglobin reductase catalyses the reduction of methylene blue to leucomethylene blue. This transfers electrons to methaemoglobin non-enzymatically, restoring functional haemoglobin and methylene blue. These reactions are sustained by the regeneration of NADPH via the hexose monophosphate shunt (pentose phosphate pathway). In the absence of methylene blue, NADPH methaemoglobin reductase contributes only some 6% to the methaemoglobin reducing capacity of the red cell, the remainder achieved mainly by an NADH dependent reductase that is not affected by methylene blue.

In otherwise healthy individuals methaemoglobin concentrations less than 25–30% often do not require specific treatment, since the patient has only minor or no symptoms and the methaemoglobin concentration will be reduced to normal over several hours by the intrinsic activity of methaemoglobin reductase. Anaemic patients or those with underlying cardiac or pulmonary disease might develop clinical features at lower methaemoglobin concentrations. When there are symptoms of respiratory distress, treatment with methylene blue is indicated.

Methylene blue 2 mg/kg body weight should be administered intravenously over 5–10 minutes as a 1% solution (methylene blue can also be diluted with 0.9% saline for infusion). Symptomatic improvement usually occurs within 30 minutes. A second 2 mg/kg dose may need to be administered in very severe cases, if there is evidence of continuing chemical absorption or prolonged methaemoglobin formation. The latter is associated

> **Box 4: Management of occupational methaemoglobinaemia**
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> ► Removal of the affected individual from further exposure
> ► Decontamination of clothes and skin
> ► Supportive measures including oxygen if there is respiratory distress
> ► Consideration of intravenous methylene blue
> ► Investigation of the workplace factors that may have contributed to over exposure to the causative chemical
> ► Implementation of health and safety measures to prevent recurrence

particularly with methaemoglobinaemia caused by poisons that require metabolic activation, such as aniline. A long half life and enterohepatic circulation of the parent compound and its metabolites may also contribute to prolonged methaemoglobin formation. If a second dose of 2 mg/kg methylene blue is administered, the clinical situation should be re-evaluated before any further dose is given, since higher or repeated doses of methylene blue may exacerbate methaemoglobin formation and cause intravascular haemolysis.[27]

An absolute contraindication to methylene blue administration is severe renal impairment since methylene blue is eliminated predominantly renally. Methylene blue may also be less effective or ineffective where NADPH availability is reduced and in the presence of intravascular haemolysis.

Individuals with glucose-6-phosphate dehydrogenase deficiency lack NADPH since glucose-6-phosphate dehydrogenase is required for the pentose phosphate enzyme pathway of NADPH production. These individuals are also more susceptible to erythrocyte oxidative stress since NADPH is needed to maintain reduced glutathione, an intrinsic protector against oxidative damage. In NADPH deplete individuals there may be a degree of competition for NADPH between glutathione striving to protect against toxin induced haemolysis and methylene blue serving to protect against methaemoglobinaemia. In these patients methylene blue may not only be ineffective but may also exacerbate haemolytic anaemia.

Optimal methaemoglobin reduction by methylene blue operates in intact erythrocytes whereas the presence of haemolysis favours methylene blue induced methaemoglobin formation.[28] Haemolysis results in the enzymatic destruction of NADPH, and without NADPH, methaemoglobin

reduction cannot occur. Therefore, chemicals that cause haemolysis, such as chlorates and anilines, may be "resistant" to methylene blue treatment. Since excess methylene blue may exacerbate haemolysis it is advisable not to exceed a total intravenous dose of 4 mg/kg body weight in these patients without seeking specialist advice.

Rapid injection of methylene blue may be painful and extravasation has caused tissue necrosis.[29][30] Secure venous access should therefore be ensured before methylene blue administration. The administration of intravenous methylene blue 7 mg/kg to individuals *without* methaemoglobinaemia has been associated with nausea and vomiting, tachypnoea, chest tightness, tachycardia, apprehension, tremor, mydriasis, blue staining of the skin and mucous membranes, abdominal pain, dizziness, paraesthesiae, headache, confusion, mild methaemoglobinaemia (up to 7%) and ECG changes (T wave flattening or inversion).[31] These features resolved within 2–12 hours of the injection. In another report 5 mg/kg intravenous methylene blue administered as a diagnostic dye caused 7% methaemoglobinaemia.[32]

In high dose (20–30 mg/kg) methylene blue has precipitated severe intravascular haemolysis.[33][34] Lower doses may exacerbate methaemoglobinaemia and/or intravascular haemolysis, particularly following exposure to agents which themselves cause haemolysis, notably chlorates and aniline related compounds.

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### Box 5: Methylene blue as an antidote for methaemoglobinaemia

▶ Indicated if methaemoglobin concentrations are above 25–30% (lower concentrations usually associated with minor symptoms or an absence of symptoms)
▶ Dose: 2 mg/kg body weight administered intravenously as a 1% solution over 5–10 minutes. Second dose may be required for severe cases
▶ Mechanism of action: acts as a reducing agent to convert methaemoglobin to haemoglobin

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## Conclusions

Occupational methaemoglobinaemia is uncommon and severe cases are rare. Most cases involve dermal and/or inhalational exposure to amino or nitro substituted benzenes and related compounds. Knowledge of chemicals with the potential to oxidise haemoglobin plus effective workplace measures to minimise exposure will help prevent occupational cases. Prompt diagnosis and treatment with intravenous methylene blue in cases with severe symptoms is necessary for a favourable prognosis.

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**QUESTIONS (See answers on page 589)**

**(1)** Recognised causes of methaemoglobinaemia include:
- *(a)* sodium nitrite
- *(b)* trivalent chromium compounds
- *(c)* sodium chlorate
- *(d)* potassium ferricyanide
- *(e)* aniline

**(2)** Recognised features of methaemoglobinaemia include:
- *(a)* cherry pink skin colour
- *(b)* "slate grey" cyanosis
- *(c)* sinus tachycardia
- *(d)* dyspnoea
- *(e)* "metallic" taste in mouth

**(3)** The following make a diagnosis of methaemoglobinaemia more probable:
- *(a)* a history of occupational exposure to dinitrophenol
- *(b)* cyanosis disproportionate to the extent of respiratory distress
- *(c)* a haemoglobin concentration of less than 9 g/dl
- *(d)* chocolate brown discolouration of arterial blood
- *(e)* a reduced partial pressure of oxygen in arterial blood

**(4)** The administration of intravenous methylene blue 2 mg/kg in the treatment of occupational methaemoglobinaemia:
- *(a)* may result in pain at the site of injection
- *(b)* is a priority if the methaemoglobin concentration is 20% of total haemoglobin
- *(c)* is less efficacious in the presence of intravascular haemolysis
- *(d)* is ineffective more than four hours post-exposure
- *(e)* typically leads to symptomatic improvement after a latent period of 1–2 hours

**(5)** Recognised absolute contradictions to the use of methylene blue in the treatment of methaemoglobinaemia include:
- *(a)* respiratory distress
- *(b)* plasma creatinine concentration of 200 µmol/l
- *(c)* ALT activity of 500 IU/l
- *(d)* glucose-6-phosphate dehydrogenase deficiency
- *(e)* haemoglobin concentration of 9 g/dl

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